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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/052,641	01/23/2002	Karl-Heinz Heider	0652.1910001	3959

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EXAMINER	
HELMS, LARRY RONALD	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 03/10/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/052,641	HEIDER ET AL.	
	Examiner	Art Unit	
	Larry R. Helms	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 17-22 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 17-22 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 09/331,254.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 8/13/02.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 17-22 are pending and under examination

Specification

2. The disclosure is objected to because of the following informalities: The first line of the specification needs to be updated to indicate application 09/331,254 is now US Patent 6,372,441.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 17-22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 17-22 are indefinite for reciting the phrase "pharmaceutically acceptable amount" in claim 17 because it is unclear what the amount is intended for. The phrase is indefinite when the claims fails to state the function which is to be achieve. In re Frederiksen, 213 F 2d 547, 102 USPQ 35 (CCPA 1954).

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 17-22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a pharmaceutical composition comprising an antibody for the protein encoded by the variable exon v10 of the CD44 gene and the composition is in freeze dried form, does not reasonably provide enablement for a pharmaceutical composition comprising an antibody for the protein encoded by the variable exon v10 of the CD44 gene and an adjuvant. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The claims are broadly drawn to a pharmaceutical composition comprising an antibody and an adjuvant. The claims broadly read on a vaccine, i.e. an antibody and an adjuvant for therapy.

The specification provides no exemplification of or guidance on how to use the vaccine formulation for active immunotherapy in humans. The goal of tumor vaccination

is the induction of tumor immunity to prevent tumor recurrence and to eliminate residual disease. However, Ezzell (J. NIH Res, 1995, 7:46-49) reviews the current thinking in cancer vaccines and states that tumor immunologists are reluctant to place bets on which cancer vaccine approach will prove effective in the long run (see the entire document, particularly last paragraph) and further states that no one is very optimistic that a single peptide will trigger an immune response strong enough to eradicate tumors or even to prevent the later growth of micrometastases among patients whose tumors have been surgically removed or killed by radiation or chemotherapy (p 48, para 6). In addition, Spitler (Cancer Biotherapy, 1995, 10:1-3) recognizes the lack of predictability of the nature of the art when she states that "Ask practicing oncologists what they think about cancer vaccines and you're likely to get the following response: "cancer vaccines don't work". Ask a venture capitalist or the director of product development at a large pharmaceutical company and you're likely to get the same response." (p 1, para 1).

Furthermore, Boon (Adv Can Res, 1992, 58:177-210) teaches that for active immunization in human patients we have to stimulate immune defenses of organisms that have often carried a large tumor burden. Establishment of immune tolerance may therefore have occurred and it may prevent immunization and several lines of evidence suggest that large tumor burdens can tolerize or at least depress the capability to respond against the tumor (p. 206, para 2).

Therefore, in view of the lack of guidance in the specification and in view of the discussion above one of skill in the art would be required to perform undue experimentation in order to practice the claimed invention.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 17-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ghaffari et al (Blood 86:2976-85, 1995, IDS 8/13/02) or Herold-Mende et al (J of Pathology 179:66-73, 5/96) or Manten-Horst et al (Int. J. Cancer 64:182-188, 1995) and further in view of Robinson et al (U.S. Patent 5618920, filed 4/94), Adair et al (WO 91/09967, published 7/91), Mackay et al (The Journal of Cell Biology 124:71-82, 1994, IDS 8/13/02), Savage et al (Br. J. Cancer 76:304-310, 1993, IDS 8/13/02) and Andya et al (US Patent 6685940, priority to 7/95).

The claims recite a pharmaceutical composition comprising a pharmaceutically acceptable amount of an antibody specific for SEQ ID NO:2 which is an amino acid sequence encoded by the variable exon v10 of CD44 and is in freeze-dried form and the antibody is a monoclonal or humanized recombinant and the antibody is linked to a radioisotope or cytokine. For this rejection the intended use of the antibody as a pharmaceutical is given no patentable weight.

All of Ghaffari et al, Manten-Horst et al, and Herold-Mende et al teach antibodies specific for v10 of CD44 (see materials and Methods) and the CD44v10 is implicated in cancer and detected with the antibody. All of Ghaffari et al, Manten-Horst et al, and Herold-Mende et al do not teach a freeze-dried form or a labeled antibody or a Fab fragment or a recombinant antibody or a molecule linked to a cytokine. These deficiencies are made up for in the teachings of Robinson et al, Adair et al, Mackay et al, Savage et al, and Andya et al.

Andya et al teach protein formulations for freeze-drying antibodies (see Example 1).

Mackay et al teach "CD44 and CD44 variants can be modulated by certain cytokines." (See page 78) and "Expression of the epithelial variant...(10v containing isoforms) was also slightly down regulated by cytokine treatment" (see page 78).

Savage et al teach a single chain antibody linked to an IL-2 polypeptide (see abstract).

Robinson et al teach determination of nucleic acids encoding VH and VL of any known antibody and use of said VH and VL to produce antibody fragments (see column 1-45, and columns 12-22). Robinson et al teach that "The invention also produces consensus sequences and specific oligonucleotide sequences useful as probes for hybridization and priming cDNA synthesis of any hybridoma mRNA coding for variable regions of any desired specificity." (see column 4, last paragraph).

Adair et al teach humanization of antibodies and labeling with isotopes and therapy with the antibodies.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have used the antibody of Ghaffari et al, Manten-Horst et al, or Herold-Mende et al and freeze dry the antibody as taught by Andya et al and produce a recombinant humanized antibody using the hybridoma and obtaining the nucleotide sequence as taught by Robinson and humanize the antibody as taught by Adair et al and add a label or produce an IL-2 fusion protein as taught by Savage et al and Mackay et al.

One of ordinary skill in the art would have been motivated and have a reasonable expectation of success in using the antibody of Ghaffari et al, Manten-Horst et al, or

Herold-Mende et al and freeze dry the antibody as taught by Andya et al and produce a recombinant humanized antibody using the hybridoma and obtaining the nucleotide sequence as taught by Robinson and humanize the antibody as taught by Adair et al and add a label or produce an IL-2 fusion protein as taught by Savage et al and Mackay et al because Andya et al teach freeze-dry formulations which can be reconstituted to a high protein concentration without loss in stability of the protein (see abstract). In addition, one of ordinary skill in the art would have been motivated and have a reasonable expectation of success in using the antibody of Ghaffari et al, Manten-Horst et al, or Herold-Mende et al and freeze dry the antibody as taught by Andya et al and produce a recombinant humanized antibody using the hybridoma and obtaining the nucleotide sequence as taught by Robinson and humanize the antibody as taught by Adair et al and add a label or produce an IL-2 fusion protein as taught by Savage et al and Mackay et al because It would have been obvious to obtain the amino acid sequence of the antibody of Ghaffari et al, Manten-Horst et al, or Herold-Mende et al from the hybridoma as taught by Robinson et al because it was routine at the time to clone the nucleotide sequence of the mRNA from the hybridoma of an antibody producing cell as taught by Robinson. In addition, one of ordinary skill in the art would have been motivated and have a reasonable expectation of success in using the antibody of Ghaffari et al, Manten-Horst et al, or Herold-Mende et al and freeze dry the antibody as taught by Andya et al and produce a recombinant humanized antibody using the hybridoma and obtaining the nucleotide sequence as taught by Robinson and humanize the antibody as taught by Adair et al and add a label or produce an IL-2

fusion protein as taught by Savage et al and Mackay et al because Savage et al teach "this fusion protein, in addition to retaining antigen binding ability, possesses the immuno-stimulatory action of IL-2 when tested with lymphocytes bearing the high affinity IL-2 receptor." (See page 304). In addition, it would have been obvious because Mackay et al teach "CD44 and CD44 variants can be modulated by certain cytokines." (See page 78) and "Expression of the epithelial variant...(10v containing isoforms) was also slightly down regulated by cytokine treatment" (see page 78). Thus, it would have been obvious to produce a composition that is freeze-dried with the antibody or a humanized form of the antibody or a antigen binding fragment thereof linked to a radiolabel or a cytokine.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Conclusions

9. No claim is allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Larry R. Helms, Ph.D, whose telephone number is (571) 272-0832. The examiner can normally be reached on Monday through Friday from 7:00 am to 4:30 pm, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, can be reached at (571) 272-0871.

11. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Fax Center telephone number is 703-872-9306.

Respectfully,

Larry R. Helms Ph.D.

571-272-0832